**REMARKS**

Claims 119, 126, 127 and 129-142 are pending in the subject application. Applicants hereinabove have amended the specification and amended claims 119, 126, 127, 129-132, 135, 141, and 142. Accordingly, upon entry of this Amendment, claims 119, 126, 127 and 129-142, as amended, will still be pending and under examination.

Applicants have amended claim 135 to correct a minor typographical error. Applicants maintain that the amendments to the specification and to claims 119, 126, 127, 129-132, 141, and 142 do not raise any issue of new matter, and that these claims, as amended, are fully supported by the specification as originally filed.

Support for the claim amendments is found, *inter alia*, in the specification as follows: **Claims 119 and 129-132**: page 11, line 33 to page 12, line 29, page 12, lines 15-16, page 14, lines 1-5, page 32, lines 13-20, and Figures 1-1 and 1-2; **Claim 126**: page 87, lines 27-29, and page 37, lines 31-35; **Claims 127, 141 and 142**: page 12, lines 15 and 16, page 16, lines 26-28, and page 66, lines 8-14.

In view of the comments set forth below, applicants maintain that the grounds of the Examiner's rejections made in the April 16, 2004 Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw these grounds of rejection.

**February 3, 2004 Examiner's Proposed Amendment, February 6, 2004 Examiner's Interview and August 12, 2004 Examiner's Interview**

On February 3, 2004, the Examiner forwarded to the undersigned's office a proposed Examiner's Amendment for the subject application and for related copending applications (U.S. Serial Nos. 08/477,097 and 08/481,809) which applicants understood would place this application in condition for allowance. Applicants note for the record their appreciation for the courtesies extended by Examiner Holleran to their representatives, John P. White, Esq. and Mark A. Farley, Esq., in providing the proposed Examiner's Amendment. For completeness of the record, applicants submit herewith as **EXHIBITS A** and **B** copies of the February 3, 2004 Examiner's Proposed Amendments in connection with related U.S. Serial Nos. 08/477,097 and 08/481,809, respectively.

On February 6, 2004, applicants' undersigned attorney, Mark A. Farley, Esq., had a telephonic interview with Examiner Holleran concerning the February 3, 2004 Examiner's Proposed Amendment in connection with this application and related copending applications (U.S. Serial Nos. 08/477,097 and 08/481,809). Applicants again wish to thank the Examiner for her time and consideration during this interview. For completeness of the record, applicants submit herewith as **EXHIBITS C** and **D** copies of the February 3, 2004 Examiner's Proposed Amendments in connection with related U.S. Serial Nos. 08/477,097 and 08/481,809, respectively.

Subsequently, on April 16, 2004, Examiner Holleran issued the Office Action to which this Amendment is a response.

Thereafter, on August 12, 2004, the undersigned had a telephonic interview with Examiner Holleran concerning the February 3, 2004 Examiner's Proposed Amendment. Applicants again wish to thank the Examiner for her time and consideration during this interview.

Applicants have carefully reviewed the February 3, 2004 proposed Examiner's Amendment and have substantially incorporated it into this Amendment. However, applicants have made certain changes which are believed necessary, for example, to correct minor typographical errors and to insure proper antecedent basis in the amended claims. Applicants maintain that this Amendment places this application in condition for allowance and look forward to receiving from the Examiner a communication to this effect.

**Rejections Withdrawn In The April 16, 2004 Office Action**

The Examiner also stated that the objection to the disclosure is withdrawn in view of applicants' submission of a new "Figure 6B."

The Examiner stated that the provisional rejection of claims 119-143 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 101-126 of copending Serial No. 08/477,097 is withdrawn in view of the terminal disclaimer filed December 15, 2003.

The Examiner also stated that the rejection of claims 122-124 and 143 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, is withdrawn in view of the cancellation of claims 122-124 and 143.

The Examiner also stated that the rejection of claims 119-129 under 35 U.S.C. §103(a) as being unpatentable over Wiegand et al. (U.S. Patent 5,599,914, issued February 4, 1997) in view of Fiume et al. (Critical Rev. Therapeutic Drug Carrier Systems, 4(4):265-284 (1988)), Ritter et al. (Seminars in Cancer Biology, 2:401-409 (1991)), Kensil et al. (The Journal of Immunology, 146(2):431-437 (1991), Marciani et al. (Vaccine, 9:89-96 (1991)) and Uemura et al. (J. Biochem., 79(6):1253-1261 (1976)) is withdrawn.

The Examiner also stated that the rejection of claims 119, 129-132 and 134-143 under 35 U.S.C. §103(a) as being unpatentable over Wiegand et al. (U.S. Patent 5,599,914, issued February 4, 1997), Fiume et al. (Critical Rev. Therapeutic Drug Carrier Systems, 4(4):265-284 (1988)), Livingston et al. (Cancer Research, 149:7045-7050 (1989)), in view of Ritter et al. (Seminars in Cancer Biology, 2:401-409 (1991)), Livingston et al. (U.S. Patent No. 5,102,663), Kensil et al. (The Journal of Immunology, 146(2):431-437 (1991), Marciani et al. (Vaccine, 9:89-96 (1991)) and Uemura et al. (J. Biochem., 79(6):1253-1261 (1976)) is withdrawn.

The Examiner further stated that the rejection of claims 132 and 133 under 35 U.S.C. §103(a) as being unpatentable

over Wiegand et al. (U.S. Patent 5,599,914, issued February 4, 1997) in view of Fiume et al. (Critical Rev. Therapeutic Drug Carrier Systems, 4(4):265-284 (1988)), Livingston et al. (Cancer Research, 149:7045-7050 (1989)), Ritter et al. (Seminars in Cancer Biology, 2:401-409 (1991)), Livingston et al. (U.S. Patent No. 5,102,663), Kensil et al. (The Journal of Immunology, 146(2):431-437 (1991), Marciani et al. (Vaccine, 9:89-96 (1991)), and Uemura et al. (J. Biochem., 79(6):1253-1261 (1976)) as applied to claims 78, 80-92, 94 and 96-99 (applicants understand this to mean claims *119, 129-132* and *134-143*) above and further in view of Irie et al. (U.S. Patent No. 4,557,931) is withdrawn.

**Formalities**

The Examiner objected to claims 126 and 129 under 37 C.F.R. §1.75(b) because claims 126 and 129 appear to claim inventions of the same scope.

In response, applicants point out that claim 126, as amended above, now recites "50 µg." Thus, applicants maintain that the Examiner's objection to claims 126 and 129 has been obviated.

**Provisional Obviousness-Type Double Patenting**

The Examiner provisionally rejected claims 119, 126, 127 and 129-143 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending U.S. Application No. 08/477,147 was reinstated because the claims in U.S. Application No.

08/477,147 have been amended so that they are now drawn to conjugates comprising a GM2 ganglioside.

In response to this *provisional* rejection, applicants intend to submit a substitute Terminal Disclaimer with respect to any patent issuing from any one or more of copending U.S. Serial Nos. 08/475,784, 08/477,097, 08/477,147 and/or 08/481,809 in the near future. Applicants note that the substitute Terminal Disclaimer will replace and supersede in all respects the Terminal Disclaimer filed December 15, 2003.

**Claim Rejection Under 35 U.S.C. §112, First Paragraph - Written Description**

The Examiner rejected claims 119, 126, 127 and 129-142 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner stated that the specification does not support the genus of conjugates comprising gangliosides, wherein the ganglioside has "an altered ceramide portion comprising an altered sphingosine base."

The Examiner stated that the claimed inventions read on compositions comprising ganglioside conjugates and methods of treatment comprising the administration of compositions comprising ganglioside conjugates, where the ganglioside portions of the conjugates are so broadly claimed that they are not adequately described by the

specification. Specifically, the Examiner stated that the recitation "ganglioside derivative" that comprises "an altered ceramide portion comprising an altered sphingosine base" refers to a genus of compounds that is not supported by the specification. The Examiner stated that the only example of an "altered ceramide portion comprising an altered sphingosine base" provided by the specification is the one example of a ganglioside conjugate in which, prior to conjugation, the sphingosine base has been cleaved with ozone and reduced to form a reactive aldehyde at the C-4 carbon of the sphingosine base. The Examiner also stated that this one example is not representative of all the possible species encompassed by the phrase "ganglioside derivative" which comprises "an altered ceramide portion comprising an altered sphingosine base." The Examiner thus concluded that the genus of conjugates is not supported by an adequate written description of the varied members of the genus, and one of skill in the art would not find that applicants were in possession of the genus of claimed compositions or claimed methods using the claimed compositions at the time of filing.

In response to the Examiner's rejection to claims 119, 126, 127 and 129-142, but without conceding the correctness thereof, applicants note that claims 119, 126, 127, 129-132, 135, 141, and 142 have been amended. These claims, as amended, do not recite the phrase "an altered ceramide portion comprising an altered sphingosine base." Instead, they only refer to an altered sphingosine base, the nature of the alteration being further defined elsewhere in the claim.

In view of the amendments to the claims, applicants maintain that claims 119, 126, 127 and 129-142 satisfy the requirements of 35 U.S.C. §112, first paragraph, and request that the Examiner reconsider and withdraw this ground of rejection.

**Claim Rejection Under 35 U.S.C. §112, Second Paragraph - Indefiniteness**

The Examiner rejected claims 119, 126, 127 and 129-142 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner stated that claims 119, 129, 131 and 132 are indefinite because of the recitation of "QS-21". The Examiner stated that the specification does not describe with sufficient clarity the chemical and structural nature of "QS-21". The Examiner stated that the specification appears to define QS-21 as an example of saponins that may be extracted from the bark of a Quillaja saponaria Molina tree, and to reference literature that teaches one how to isolate QS-21 from a mixture of saponins. The Examiner also stated that because QS-21 appears to be an essential ingredient of the claimed invention, the attempt to describe QS-21 and how it is isolated is an attempt by incorporation by reference of matter essential to the practice of the claimed invention. The Examiner further stated that the references cited are not available for incorporation by reference because they are non-patent publications.

In response to the Examiner's rejection to claims 119, 126, 127 and 129-142, but without conceding the correctness thereof, applicants, as proposed by the Examiner in the February 3, 2004 Examiner's Proposed Amendment, have hereinabove amended the specification to incorporate explicitly subject matter previously incorporated by reference from Kensil, et al. "Separation and Characterization of Saponins with Adjuvant Activity from *Quillaja saponaria* Molina Cortex", Journal of Immunology, 146(2):431-437 (January 15, 1991) and Newman, et al., "Saponin Adjuvant Induction of Ovalbumin-Specific $CD8^+$ Cytotoxic T Lymphocyte Responses", Journal of Immunology, 148(8):2357-2362 (April 15, 1992). Kensil, et al. and Newman, et al. are expressly incorporated on page 66, line 10 and page 128, lines 27-34 of the specification, and are designated as reference numbers "10" and "11", respectively, in the Third Series of Experiments.

Specifically, applicants have amended the specification to incorporate the first two paragraphs of the "Materials And Methods" section on page 432 of Kensil, et al. and footnote 2 on page 2357 of Newman, et al.

In accordance with M.P.E.P. §608.01(p)(I)(A)(2), applicants' undersigned attorney states that the amendatory material from Kensil, et al. and Newman, et al. consists of the same material incorporated by reference in the referencing application, and that the specification, as amended, does not raise any issue of new matter.

In view of the above remarks, applicants maintain that amended claims 119, 126, 127 and 129-142 satisfy the requirements of 35 U.S.C. §112, second paragraph, and request that the Examiner reconsider and withdraw this ground of rejection.

The Examiner also rejected to claims 119, 126, 127, 129, 130, 132 and 141 under 35 U.S.C. §112, second paragraph as allegedly indefinite because of the phrase "the saponin", which lacks antecedent basis in the claim.

In response to the Examiner's rejection to claims 119, 126, 127, 129, 130, 132 and 141, applicants note that these claims, as amended, do not recite the phrase "the saponin." Instead, they only refer to "QS-21."

In view of the above remarks, applicants maintain that amended claims 119, 126, 127, 129, 130, 132 and 141 satisfy the requirements of 35 U.S.C. §112, second paragraph, and request that the Examiner reconsider and withdraw this ground of rejection.

**Rejections Under 35 U.S.C. §103(a) - Obviousness**

The Examiner rejected claims 119, 131, 132 and 134-142 under 35 U.S.C. §103(a) as allegedly unpatentable over Wiegand (U.S. Patent No. 5,599,914, issued February 4, 1997) in view of Jennings (U.S. Patent No. 4,356,170, issued October 26, 1982), in view of Neurath (U.S. Patent No. 4,591,552, issued May 27, 1986), in view of Ratcliff (U.S. Patent No. 5,344,870, issued September 6, 1994), in view of Patrick (U.S. Patent No. 4,652,629, issued March

24, 1987), in view of Blincko (U.S. Patent No. 5,256,409, issued October 26, 1993), in view of Marciani (Vaccine, 9:89-96 (February 1991)), in view of Ritter (Seminars in Cancer Biology, 2:401-409 (1991)) and further in view of Livingston (Proc. Natl. Acad. Sci. USA, 84:2911-2915 (May 1987)).

The Examiner stated that Wiegand discloses glycoconjugates comprising gangliosides conjugated to carrier proteins, wherein the ganglioside has been ozonolyzed and reduced at the C-4 double bond of the sphingosine base to produce a reactive aldehyde intermediate that may be reacted directly with free amines present in carrier proteins to form a conjugate (citing to col. 1, line 11 to col. 2, line 44), wherein the ganglioside may be GM3, GD3, GM2 or GM1. The Examiner stated that Wiegand teaches that the coupling of gangliosides to carrier proteins is appropriate of all gangliosides, and that glycoconjugates of gangliosides are useful as vaccines (citing col. 2, lines 50-55). The Examiner acknowledged that Wiegand fails to explicitly teach that the bond between the aldehyde group of ozonolyzed and reduced ganglioside and the carrier protein would be via a lysine residue of the carrier protein. The Examiner also acknowledged that Wiegand fails to specifically teach a glycoconjugate comprising the specific carrier protein, KLH, and fails to teach a glycoconjugate having a ganglioside to KLH molar ratio of about 200:1 to 1400:1. The Examiner also acknowledged that Wiegand fails to teach a glycoconjugate within a composition containing a saponin. The Examiner also acknowledged that Wiegand fails to teach the specific

range of amounts of conjugated ganglioside in a composition, where the amounts are about 1μg to about 200μg.

The Examiner stated that Jennings discloses the chemistry of linking a carbohydrate containing a reactive aldehyde group to a carrier protein is well known and likely would be via a lysine (citing col. 3, lines 40-46 and claims 11 and 18 at cols. 9 and 10, respectively).

The Examiner stated that Ratcliff, Patrick and Blincko disclose that KLH was known as a useful carrier protein for carbohydrate antigens (citing Ratcliff, col. 29, lines 46-51), small peptide antigens (citing Patrick, col. 9, lines 7-28), and for tricyclic antidepressant drugs (citing Blincko, col. 7, lines 29-41).

The Examiner stated that Ritter discloses the desirability of conjugating gangliosides to KLH. The Examiner stated that Ritter discloses that covalent attachment to KLH results in the production of IgG antibodies in melanoma patients, and that the production of IgG antibodies is desirable because IgG antibodies are of higher affinity, better able to penetrate solid tissue, able to mediate antibody-dependent cell-mediated cytotoxicity and remains in the circulation for longer periods after immunization (citing page 106, 1st col.).

The Examiner stated that Neurath, using KLH as the carrier protein and the SPDP heterobifunctional linker method of Wiegand, discloses peptide-KLH conjugates contain approximately 200 peptide molecules per KLH

(citing col. 17, lines 15-40).

The Examiner thus concluded that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention was made to have made the conjugates of the claimed composition, wherein the conjugates comprise a GM2 ganglioside covalently bound to via lysine residues of KLH, a well-known carrier protein, by reductive amination as taught by Jennings, and to have achieved a ganglioside-KLH molar ratio of between 200:1 to 1400:1, because Neurath teaches that a molar ratio of hapten to carrier protein of 200:1 can be achieved using KLH and using a method that attaches the hapten to KLH via lysine residues.

The Examiner also acknowledged that Wiegand fails teach a glycoconjugate within a composition containing a saponin. However, the Examiner stated that Marciani teaches that the use of 20μg of QS-21 as an adjuvant in a genetically-engineered subunit vaccine against feline leukemia virus, and teaches that the choice of QS-21 was important in achieving an immunogenic response to the recombinant viral peptide in that QS-21 was much more effective that alum or oil emulsions in eliciting a humoral response and were protected from viral challenges (citing page 94, col. 2, 2nd full paragraph to page 95, col. 1). The Examiner therefore concluded that it would have been prima facie obvious to one of ordinary skill in the art to have used an adjuvant such as QS-21 because QS-21 appears to be superior to other art known adjuvants such as alum and oil emulsions.

The Examiner further acknowledged that Wiegand also fails to teach the specific range of amounts of conjugated ganglioside in a composition, where the amounts are about 1μg to about 200μg. However, the Examiner stated that Livingston teaches immunization of human melanoma patients with a dose of 100μg of an unconjugated GM2 ganglioside preparation (combined with BCG or S. Minnesota mutant R595) that produced an antibody response (citing page 2912, col. 2 to page 2913, and Table 2). The Examiner thus concluded that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have determined the appropriate amounts of KLH-conjugated ganglioside to administer.

The Examiner also stated that the claimed invention is also drawn to methods of treatment, either a method of stimulating or enhancing production of an antibody of GM2, or a method of treating a human subject having cancer comprising the administration of compositions comprising GM2 ganglioside conjugates. The Examiner stated that Wiegand suggests such methods because it teaches that ganglioside conjugates may be used as vaccines. The Examiner also stated that Livingston and Ritter both teach that melanoma patients respond to preparations comprising gangliosides and adjuvants by producing ganglioside and melanoma specific antibodies. The Examiner thus concludes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention was made to use the ganglioside compositions comprising a conjugate of Wiegand where the carrier protein is KLH, as suggested by Ritter (and also

Ratcliff, Patrick and Blincko) and further comprising an adjuvant such as QS-21 as taught by Marciani in methods of treatment for the production of GM2 ganglioside antibodies, or for the treatment of a human subject having cancer. The Examiner also concluded that optimization of the dosage, route of immunization, number of sites of immunization to administer the composition is well within the skill of the ordinary artisan.

In response to Examiner's above rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims.

Briefly, claim 119, as amended, provide a composition which comprises (A) a conjugate of (i) a derivative of a GM2 ganglioside which GM2 ganglioside comprises an unaltered sphingosine base, wherein the derivative differs from the GM2 ganglioside solely by having an altered sphingosine base which retains only C1 through C4 from the unaltered sphingosine base of the GM2 ganglioside, and (ii) Keyhole Limpet Hemocyanin, wherein the GM2 ganglioside derivative is covalently bound to Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the altered sphingosine base and a nitrogen of an ε-aminolysyl group of Keyhole Limpet Hemocyanin; (B) QS-21; and (C) a pharmaceutically acceptable carrier; wherein the amount of the conjugated GM2 ganglioside derivative is an amount between about 1 µg and about 200 µg, the amount of QS-21 is an amount between about 10 µg and about 200 µg, the GM2:Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1,

and the relative amounts of such conjugate and QS-21 is effective to stimulate or enhance production in a subject of an antibody to the GM2 ganglioside. Claims 131, 132 and 134-142, as amended, provide for methods of stimulating or enhancing production of an antibody directed to the GM2 ganglioside in a subject, and methods of treating a human subject having cancer, e.g., melanoma, by administering said composition to the subject.

The claimed invention is based on applicants' *surprising discovery* that GM2-KLH, with QS-21 as an adjuvant, is a strikingly immunogenic vaccine, far superior to previous ganglioside-based vaccines, such as GM2 adherent to the surface of BCG, salmonella Minnesota mutant R595 or proteosomes, GM2-KLH only, and GM2-KLH plus DETOX or BCG, with regard to (1) higher IgM and IgG antibody titers against GM2 and (2) a decrease in systemic and local adverse reactions related to administrating to a subject. See instant specification, page 58, line 24 to page 59, line 19, and page 93, line 16 to page 95, line 15.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest each element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

The references cited against the rejected claims fail to

support a *prima facie* case of obviousness. Here, the cited references fail to support a *prima facie* case of obviousness. Specifically, to support a *prima facie* case of obviousness, one of ordinary skill would have to have been motivated to combine the teachings of the cited references at the time of the invention. Moreover, these references would also have to provide a reasonable expectation of success.

It is stressed that the Examiner has based this rejection on the teachings of no fewer than *nine* references. Collectively, these references teach (1) a chemical modification of the sphingosine portion of glycosphingolipids and the subsequent coupling of such modified glycosphingolipids to other molecules, e.g., protein, (2) the preparation of antigenic polysaccharide-protein conjugates by directly conjugating a protein with an altered polysaccharide, (3) the use of KLH in synthesizing carbohydrate antigens, small peptide antigens and tricyclic antidepressant drugs, (4) covalent attachment of gangliosides to foreign carrier proteins, (5) a radioactive or enzyme labeled synthetic peptide conjugated to KLH which employs a *synthetic peptide:KLH molar ratio* of 200:1, (6) the use of 20μg of QS-21 as an adjuvant in a vaccine for cats against feline leukemia virus, and (7) the preparation of GM2-only, GM2/BCG or GM2/R595 vaccines using 100μg of purified, *unmodified* GM2 ganglioside. From these references, the Examiner draws the untenable conclusion that one of ordinary skill in the art would have been motivated to combine, and would have reasonably expected, this combination to work better than previous GM2-based compositions in treating cancer,

such as melanoma.

Specifically, Wiegand teaches a chemical modification of the sphingoid portion of glycosphingolipids and the subsequence coupling of such modified glycosphingolipids to other molecules, such as proteins. Wiegand also discloses the preparation and subsequent coupling of reductively aminated ozonolysis products of the *GM3, GD3, GM2 and GM1* gangliosides. Wiegand, col. 5, line 24 to col. 16. Wiegand, however, does not teach or suggest any particular species of glycosphingolipid that would perform effectively as a vaccine when linked to other molecules to form an immunoconjugate composition, such as the claimed invention. Hence, Wiegand neither describes nor suggest that the modification and conjugation of a derivative of a particular ganglioside, such as GM2 ganglioside, would produce a composition having superior immunogenic properties relative to a composition obtained with the use of any other gangliosides that are listed in the reference.

Furthermore, as acknowledged by the Examiner herself in the outstanding Office Action, Wiegand fails to explicitly teach (1) the bond between the aldehyde group of ozonolyzed and reduced ganglioside and a carrier protein would be via a lysine residue of the carrier protein, (2) a glycoconjugate comprising the specific carrier protein, KLH, (3) a glycoconjugate having a ganglioside to KLH molar ratio of about 200:1 to 1400:1, (4) a glycoconjugate within a composition containing a saponin, such as QS-21, and (5) the specific range of amounts of conjugated ganglioside in a composition, where

the amounts are about 1μg to about 200μg.

Jennings teaches the preparation of antigenic polysaccharide-protein conjugates by altering a polysaccharide molecule via controlled oxidation and specifically coupling the altered polysaccharide with a free amino group of a protein via reductive amination. Applicants respectfully disagree with the Examiner's contention that the conjugation procedure taught in Jennings, in combination with Wiegand, provides for the identical coupling procedures recited in the claimed invention. Specifically, applicants note that Jennings teaches *altering* the polysaccharide and *directly* conjugating the modified polysaccharide with a protein, e.g., tetanus toxoid TT, diphtheria toxoid and other proteins derived from bacteria, bovine serum albumin (BSA), or other proteins containing lysine residues such as a synthetic polylysine. Jennings, Abstract; col. 3, lines 3-54; col. 5, line 17 to col. 6, line 10. The claimed invention radically differs from Jennings in that (1) a ganglioside, i.e., GM2 ganglioside, is used to conjugate with the carrier protein KLH, (2) the carbohydrate portion of the ganglioside is *unaltered* throughout the conjugation process, and (3) the conjugation between the ganglioside and the carrier protein KLH does not occurs directly on the unaltered carbohydrate portion of the ganglioside, but rather, on the altered sphingosine portion of the altered ceramide portion of the ganglioside. Moreover, Jennings does not teach nor suggest KLH as a carrier protein. Thus, Jennings actually *teaches away* from the claimed invention by encouraging one skilled in the art to modify

carbohydrates and directly conjugate carrier proteins to the terminal portion of the altered carbohydrate, and use carrier proteins other than KLH.

Ratcliff, Patrick and Blincko only teach that the carrier protein KLH may be useful in the synthesis of carbohydrate antigens, small peptides antigens and for tricyclic antidepressant drugs, respectively. None of these references teach or suggest any gangliosides, such as GM2 ganglioside, let alone specifically conjugating KLH with any gangliosides. Ratcliff merely provides a general list of carriers suitable for the *synthesis of carbohydrate antigens*. Such carriers "include proteins, such as the appropriate serum albumin, such as human or bovine serum albumin, keyhole limpet hemacyanin, tetanus toxoid, and the like." Ratcliff, col. 9, lines 1-4. Ratcliff does not teach or suggest the use of a particular carrier conjugated to a ganglioside that would produce a composition having superior immunogenic properties to treat cancer, such as melanoma.

Patrick discloses a laundry list of suitable carrier proteins for creating small peptides antigens. Patrick, col. 9, lines 7-28. Similar to Ratcliff, Patrick does not teach or suggest the use of a particular carrier, i.e., KLH, conjugated to a ganglioside that would produce a composition having superior immunogenic properties to treat cancer, such as melanoma.

Blincko provides a list of carrier proteins which include "keyhole limpet haemacyanin (KLH), bovine serum albumin (BSA), human serum albumin (HSA), polytufsin or other

repeating unit polypeptides, polyamino acids or random copolymers of amino acids, or lysozyme or other enzymes." Blincko, col. 7, lines 29-37. Blincko discloses that KLH as the more preferred carrier protein since immunogens in which the carrier protein which comprises KLH are found particularly effective in raising high titre antisera. Blincko, col. 7, lines 37-42. However, applicants stress that Blincko neither teaches nor suggests a ganglioside or the conjugation of KLH to a ganglioside.

Ritter teaches that the "covalent attachment of gangliosides to foreign carrier proteins such as KLH" can induce consistent IgG antibodies to gangiosides in the mouse. Ritter, page 406, col. 1. Ritter also teaches KLH-GM2 conjugates. However, Ritter does not describe the chemical nature of the conjugate or of how to make the conjugate. Hence, Ritter neither discloses anything conjugated through the ceramide portion of a ganglioside, nor enables making a conjugate where the "GM2 ganglioside derivative is covalently bound to Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the altered sphingosine base and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin." Furthermore, Ritter does not teach or suggest (1) an adjuvant such as QS-21, (2) the 200:1 to 1400:1 GM2:KLH molar ratio, or (3) the specified amounts of conjugated GM2 ganglioside derivative recited in the rejected claims, as amended.

Neurath discloses a radioactive or enzyme labeled synthetic peptide of no more than 60 amino acids conjugated to KLH, which is employed as a diagnostic tool

to determine the presence of Hepatitis B surface antigen. Neurath discloses a *synthetic peptide:KLH* molar ratio of 200:1. Nowhere does Neurath teach or suggest any gangliosides, glycoconjugates or a ganglioside:KLH molar ratio. Furthermore, Neurath's specific teaching of a synthetic peptide-KLH molar ratio of 200:1 does not teach the range of values, i.e., "from 200:1 to 1400:1" of ganglioside-KLH molar ratios as claimed in the instant invention.

Marciani teaches the use of 20μg of QS-21 as an adjuvant in a vaccine for cats against feline leukemia virus. Marciani also teaches that the vaccine consists of a recombinant protein, rgp70D, which is a non-glycosylated protein derived from the envelope glycoprotein of FeLV subgroup A envelope gene, that is absorbed on to aluminium hydroxide and used in conjunction with QS-21. Although Marciani teaches that "the purified saponin component elicted a high titre antibody response and also induced an affinity maturation of these antibodies," applicants strongly note that this observation is strictly limited to QS-21 when used in conjunction with a feline leukemia virus vaccine for cats. Nowhere would one skilled in the art associate this reference with the claimed invention. In other words, Marciani does not teach any gangliosides, glycoconjugates or the use of QS-21 with a glycoconjugate. Therefore, Marciani does not provide a motivation to combine such reference in combination with any of the cited references. To consider otherwise would be hindsight.

Livingston discloses vaccines containing either purified

GM2 only or purified GM2 with BCG or R595 as adjuvants. Livingston also discloses the preparation of such GM2 vaccines containing 100μg of purified, *unaltered* GM2 ganglioside. Livingston, page 2912, col. 2. Livingston radically departs from the claimed invention in that it neither teaches an *altered ganglioside derivative* that is *conjugated* to *KLH* nor the use of QS-21 as an adjuvant. Furthermore, the 100μg amount taught in Livingston applies only to unaltered GM2. Without a teaching to suggest otherwise, Livingston fails to teach the limitation of "the amount of the conjugated GM2 ganglioside derivative is an amount between about 1μg to 200μg" recited in claims 119, 131, and 132, as amended.

According to the M.P.E.P. §2143.01,

> "[t]he mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination."

*In re Mills*, 916 F.2d 680 (Fed. Cir. 1990) (emphasis added). As demonstrated above, there is simply no motivation or suggestion to combine the cited references to create the instant invention. The collection of cited references is the result of the Examiner's impermissible use of hindsight to combine these references based on knowledge of the applicants' invention and underlying discovery. None of the references cited by the Examiner give any suggestion, motivation or "indication of which parameters [are] critical or [a] direction as to which of

many possible choices is likely to be successful" to one skilled in the art to create (1) a composition which comprises (A) a conjugate of (i) a derivative of a GM2 ganglioside which GM2 ganglioside comprises an unaltered sphingosine base, wherein the derivative differs from the GM2 ganglioside solely by having an altered sphingosine base which retains only C1 through C4 from the unaltered sphingosine base of the GM2 ganglioside, and (ii) Keyhole Limpet Hemocyanin, wherein the GM2 ganglioside derivative is covalently bound to Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the altered sphingosine base and a nitrogen of an ε-aminolysyl group of Keyhole Limpet Hemocyanin; (B) QS-21; and (C) a pharmaceutically acceptable carrier; wherein the amount of the conjugated GM2 ganglioside derivative is an amount between about 1 µg and about 200 µg, the amount of QS-21 is an amount between about 10 µg and about 200 µg, the GM2:Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1, and the relative amounts of such conjugate and QS-21 is effective to stimulate or enhance production in a subject of an antibody to the GM2 ganglioside, (2) methods of stimulating or enhancing production of an antibody to the GM2 ganglioside in a subject by administering said composition to the subject, or (3) methods of treating a human subject having cancer, e.g., melanoma, by administering said composition to the subject. *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). Essentially, one skilled in the art would have had to conduct undue experimentation to achieve applicants' successful yet unexpected result.

Assuming for the sake of argument that the combination of

Wiegand, Jennings, Neurath, Ratcliff, Patrick, Blincko, Marciani, Ritter and Livingston established a *prima facie* case of obviousness (which applicants vigorous dispute), applicants respectfully maintain that any such *prima facie* rejection would be rebutted by the fact that the claimed invention demonstrates an unexpected advantage, e.g., markedly superior immunogenic results when compared to previous ganglioside-based vaccines, such as GM2/BCG or GM2-KLH plus DETOX or BCG, with regard to (1) higher titers of IgM and IgG antibodies specific for GM2 even at lower doses, and (2) a decrease in systemic and local adverse reactions related to administrating to a subject.

Applicants' specification teaches that QS-21, at *any* of the dosage used, resulted in a *qualitatively different* response than those achieved with the prior art adjuvants to GM2 ganglioside. Instant specification, page 93, line 16 to page 95, line 15. The immunogenic responses achieved with the use of GM2-KLH vaccines alone or with optimal doses of BCG or DETOX were *substantially less effective* than the claimed invention which includes QS-21. For example, even at the 10μg dose, all patients who were treated with the claimed composition produced IgG antibodies detectable by dot blot immune stains against GM2. On the other hand, with the same amount as above, patients who were treated with GM2-KLH alone or with optimal doses of BCG, salmonella Minnesota mutant R595 or proteosomes had only rarely resulted in more than 1 detectable IgG response per 6 immunized patients. Instant specification, page 94, lines 20-27.

The instant specification also teaches that local

reactions to dosages of 100-200μg of QS-21 were "quite different" in terms of local adverse reactions than those seen with comparable dosages of BCG and DETOX. Instant specification, page 94, line 5. It states that the local response is more diffuse than the response generally seen with doses of DETOX or BCG inducing comparable systemic symptoms. Instant specification, page 94, lines 8-11. It additionally teaches that a surprising feature of the subjects' response to QS-21 was that several days later (at most 10 days later) the local reactions had completely abated and there was no evidence that the vaccination had been administered to that site. Instant specification, page 97, Table 6. Furthermore, at the 100μg dose, patients treated with the claimed invention showed resulted in only 2 episodes of low grade fever in 44 injections and the local inflammatory responses, which were limited to 2-4 days, did not interfere with daily activities. Instant specification, page 93, lines 29-34.

Therefore, in view of the surprising nature of this invention, one of ordinary skill in the art would *not* have been able to predict, based on the cited references, whether the claimed invention would be *more effectively* immunogenic even at low dosages, and result in a decrease in systemic and local adverse reactions. Moreover, one of ordinary skill certainly would not have reasonably expected the superior effects over to previous ganglioside-based vaccines, such as GM2/BCG or GM2-KLH plus DETOX or BCG as discussed above. To maintain otherwise would be hindsight.

In view of the above remarks, applicants maintain that

claims 119, 131, 132 and 134-142, as amended, satisfy the requirements of 35 U.S.C. §103(a).

The Examiner also rejected claims 132 and 133 under 35 U.S.C. §103(a) as allegedly unpatentable over Wiegand (U.S. Patent No. 5,599,914, issued February 4, 1997) in view of Jennings (U.S. Patent No. 4,356,170, issued October 26, 1982), in view of Neurath (U.S. Patent No. 4,591,552, issued May 27, 1986), in view of Ratcliff (U.S. Patent No. 5,344,870, issued September 6, 1994), in view of Patrick (U.S. Patent No. 4,652,629, issued March 24, 1987), in view of Blincko (U.S. Patent No. 5,256,409, issued October 26, 1993), in view of Marciani (Vaccine, 9:89-96 (February 1991)), in view of Ritter (Seminars in Cancer Biology, 2:401-409 (1991)), in view of Livingston (Proc. Natl. Acad. Sci. USA, 84:2911-2915 (May 1987)), and further in view of Irie (U.S. Patent No. 4,557,931, issued December 10, 1985).

The Examiner stated that claims 132 and 133 also read on methods of treatment of tumors of epithelial origin. The Examiner stated that the combination of Wiegand, Jennings, Neurath, Ratcliff, Patrick, Blincko, Marciani, Ritter and Livingston fail to teach treating a cancer of epithelial origin. However, the Examiner stated that Irie teaches that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinoma (citing col. 1, lines 28-31), which is an example of a tumor of epithelial origin. The Examiner thus concluded that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the ganglioside

compositions comprising a conjugate of Wiegand where the ganglioside was a GM2, where the carrier protein is KLH, as suggested by Ritter (and also Ratcliff, Patrick and Blincko) and further comprising an adjuvant such as QS-21 as taught by Marciani in methods for the treatment of a human subject having an epithelial cancer.

In response to the Examiner's rejection of claims 132 and 133, applicants respectfully traverse this rejection for the reasons provided below.

Briefly, claims 132 and 133, as amended, provide for methods of treating a human subject having cancer which comprises administering to the subject an effective amount of a composition which comprises (a) a conjugate of (i) a derivative of a GM2 ganglioside which GM2 ganglioside comprises an unaltered sphingosine base, wherein the derivative differs from the GM2 ganglioside solely by having an altered sphingosine base which retains only C1 through C4 from the unaltered sphingosine base of the GM2 ganglioside, and (ii) Keyhole Limpet Hemocyanin, wherein the GM2 ganglioside derivative is covalently bound to Keyhole Limpet Hemocyanin by a stable amine bond between the C-4 carbon of the altered sphingosine base and the nitrogen of the ε-aminolysyl group of Keyhole Limpet Hemocyanin; and (b) QS-21; and (c) a pharmaceutically acceptable carrier; wherein the amount of the conjugated GM2 ganglioside derivative is an amount between about 1 µg and about 200 µg, the amount of QS-21 is an amount between about 10 µg and about 200 µg, the GM2:Keyhole Limpet Hemocyanin molar ratio is from 200:1 to 1400:1, and the relative amounts of such

conjugate and QS-21 is effective to stimulate or enhance production in a subject of an antibody to the GM2 ganglioside and thereby treat the subject. In one embodiment, the cancer is of epithelial origin.

The references cited against claims 132 and 133 also fail to support a *prima facie* case of obviousness.

It is stressed that the Examiner has based this rejection on the teachings of no fewer than *ten* references. Wiegand, Jennings, Neurath, Ratcliff, Patrick, Blincko, Marciani, Ritter and Livingston have been discussed above.

Irie teaches that the GM2 ganglioside is found on or in tumors of a variety of histological types, including melanomas and breast carcinomas. Irie, however, does not provide the elements missing from the references discussed above, i.e., it does not disclose or suggest the claimed composition comprising a conjugate covalently bound as recited in the claims, and also including QS-21, or a method of using such composition to enhance or stimulate antibody production, to treat cancer, or to prevent relapse of melanoma in patients at risk of such relapse, or the numerical values recited in the claimed invention. For this reason, claims 132 and 133, as amended, are patentably distinct over Irie in combination of Wiegand, Jennings, Neurath, Ratcliff, Patrick, Blincko, Marciani, Ritter and Livingston.

Moreover, as discussed above, the claimed invention demonstrates an unexpected advantage, e.g., markedly

superior immunogenic results to previous ganglioside-based vaccines, such as GM2/BCG or GM2-KLH plus DETOX or BCG, with regard to (1) higher titers of IgM and IgG antibodies specific for GM2 even at lower doses, and (2) a decrease in systemic and local adverse reactions related to administrating to a subject.

In view of the above remarks, applicants maintain that claims 132 and 133, as amended, satisfy the requirements of 35 U.S.C. §103(a).

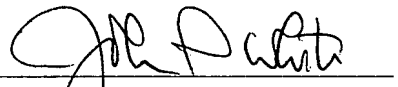
**Summary**

Applicants maintain that claims 119, 127 and 129-142, as amended, herein are now in condition for allowance. Accordingly, a notice of allowance is respectfully requested.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $490.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if an additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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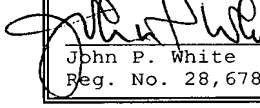

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